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ORIGINAL ARTICLE

Bone mineral density reduction in adolescents with systemic erythematosus lupus: association with lack of vitamin D supplementation

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Abstract The aim of this study is to evaluate body composition and the bone mineral density in female adolescents with juvenile systemic lupus erythematosus. Body composition (BC) and bone mineral density (BMD) were evaluated in an observational cohort study with 35 postmenarcheal adolescent females. The variables studied were as follows: current and cumulative corticosteroid dose, intake of supplements containing calcium and vitamin D, 24-h proteinuria, body mass index (BMI), and height for age (Z-score). BC was assessed using dual-energy X-ray absorptiometry (DXA) at two time points (median interval of 1.2 years). The fat mass index (FMI=fat mass in kilograms divided by the height in meters squared) and lean mass index (LMI=lean mass in kilograms divided by the height in meters squared) were calculated based on the DXA results. BMD was classified according to the International Society of Clinical Densitometry (low BMD for chronological age < −2.0 standard deviations). .The mean age of the subjects was 15.4±1.8 years. Of patients, 54.3 % were normal weight, 22.8 % were overweight, 22.8 % were obese, and 8.6 % had short stature. Low BMD for chronological age was observed in 42.8 % of patients, and 60 % were not taking vitamin D. There was no significant difference between the two time points with respect to FMI, LMI, or body mass index Z-score (ZBMI); however, BMD has decreased significantly (p=0.011). There was an association between not taking a vitamin D supplement and decreased BMD (p=0.027). Almost half of the patients had altered nutritional status. The BMD decrease in adolescents with juvenile systemic lupus erythematosus (JSLE) was associated with the lack of vitamin D supplementation, highlighting the importance of well-defined vitamin D supplementation protocols.

Keywords Adolescent · Body composition · Bone density · Densitometry · Juvenile systemic lupus erythematosus

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Introduction

In the last decade, advances in the diagnosis and treatment of juvenile systemic lupus erythematosus (JSLE) have allowed for increased patient survival, and complications that were previously infrequent have become part of the progression of the disease [1, 2]. Changes in body composition (BC), such as increased fat mass and decreased lean mass and bone mineral density (BMD), can be highlighted. These changes are multifactorial in origin and are caused by a lack of physical activity, hormonal changes, delayed puberty, increased inflammatory cytokines (e.g., interferon-γ, tumor necrosis factor), kidney impairment, nutritional disorders, vitamin D deficiency, and the intake of medications such as corticosteroids [3].

The loss of bone mass in SLE patients causes decreased BMD, damage to the tissue microarchitecture, increased bone fragility, and the consequent increased risk and prevalence of fractures [4–10].

Dual-energy X-ray absorptiometry (DXA) is the gold standard for the assessment of BC and BMD, even for the pediatric age group [11]. Most studies, using a cross-sectional design, have reported decreased BMD in the progression of JSLE patients compared with controls [12–17]. At present, only three longitudinal studies have been performed in JSLE patients with controversial results [18–20]. Trapani et al. did not report a difference in BMD after a 1-year follow-up. The

authors reported a significant and inverse correlation between the cumulative dose of corticosteroids and BMD, but no similar relationship was observed in relation to the activity or duration of the disease. On the other hand, some authors showed a reduction in BMD after 1-year follow-up in JSLE patients. This reduction, however, was not associated with any clinical parameters. These authors showed that, at disease onset, the loss of BMD is higher regardless of disease activity [18]. Lim et al. were able to predict a more intense reduction of BMD in pubertal patients at diagnosis, in patients with overweight and higher cumulative dose of steroids [19]. In both studies, neither levels nor use of vitamin D was associated with reduction of BMD in JSLE patients [18, 19].

Vitamin D deficiency is frequent in JSLE patients, ranging from 37 to 57 % [21]. Studies showing a correlation between vitamin D deficiency and bone health are scarce and highlight the need for supplementation [17].

The objective of this study was to evaluate BC and BMD in female adolescents with JSLE as well as to evaluate the influence of the severity of the disease, corticosteroid intake, and supplementation with vitamin D on BMD.

Patient selection and methods

BC and BMD were assessed by DXA in an observational cohort study with a convenience sample of postmenarcheal female adolescents (n=35) diagnosed with JSLE according to the criteria of the American College of Rheumatology and seen at the Pediatric Rheumatology outpatient clinic at the Federal University of São Paulo (Universidade Federal de São Paulo (UNIFESP)) from 2010 to 2013. Patients with other associated chronic diseases (diabetes, cardiomyopathy, endocrinopathy, or nephropathy not related to SLE) were not included. DXA was performed at two time points with an interval between 9 and 20 months (with a median of 1.2 years).

Demographic, clinical, and treatment data were collected from patient records, taking into account the medical appointments performed closest to the imaging tests. The cumulative dose of corticosteroids (oral and intravenous) was calculated. The supplementation with calcium varied according to the intake between 500 and 1200 mg daily, and vitamin D was given in a dose between 400 and 800 UI . To evaluate JSLE activity, the *Systemic Lupus Erythematosus Disease Activity Index 2000* (SLEDAI-2K) was assessed at both time points [22].

Weight and height were assessed according to World Health Organization (WHO) guidelines. For the assessment of nutritional status, body mass (body mass index Z-score (ZBMI)) and height-for-age (ZH) indices were expressed as Z-scores using the WHO AnthroPlus statistical software. Patients were categorized as overweight when the ZBMI was between 1 and 2, obese when ZBMI was >2, and having short stature when the ZH was < −2 [23].

The BC and BMD assessments were performed using DXA and always by the same trained technician from the Bone Densitometry unit at UNIFESP under the supervision of the unit's physician using the LUNAR™ DPX-MD plus device (GE-Lunar *Radiation Corporation*) equipped with software for pediatric testing (version 8.5). Different scan modes were used, taking into account the height and weight of the patients (the *slowscan* mode was used for obese patients, and *mediumscan* mode was used for the others).

For the DXA, the patients were positioned according to the standard procedure. The coefficient of variation was 2 % for the entire body. For the quality testing performed daily, a phantom provided by the manufacturer was used with a precision error of less than 1 %.

The data obtained from the DXA were used to calculate the fat mass index (FMI=total fat mass in kilograms divided by the height in meters squared) and lean mass index (LMI=total lean mass in kilograms divided by the height in meters squared) for both time points. BMD was classified according to the criteria of the *International Society of Clinical Densitometry* (low BMD for chronological age ≤ -2.0 standard deviation) [24].

Patients were routinely seen by a multidisciplinary staff, who recommended the intake of three portions of milk (or dairy products) per day and engaging in physical activity.

A free and informed consent form was signed by the patients and their legal representatives. The study was approved by the UNIFESP Research Ethics Committee.

The IBM® SPSS® Statistics version 20.0 software was used for the statistical analysis. The continuous variables were tested for normality using the Shapiro-Wilk test. For the comparison between the first and second time points, the Wilcoxon test was used for the non-parametric variables, Student's paired t test was used for the parametric variables, and McNemar's test was used for the categorical variables. An α smaller than 5 % ($p<0.05$) was used to indicate statistical significance.

Results

The adolescents included in the study had a mean age of 15.4 ±1.8 years; they had been receiving treatment for JSLE for an average of 3.7 years (range, 0.4 to 11.0 years), and the median interval between the two assessments was 1.2 years (range, 0.9 to 2.0 years) (Table 1).

At the initial time point, the SLEDAI-2K was >4 in 16 patients (45.7 %), and none had a SLEDAI-2 K >10. No patients had proteinuria at the time of the assessments, and the median cumulative dose of corticosteroids at the second assessment was 13.8 g (range, 8.7 to 19.3 g). Eighteen of the 35 patients (51.4 %) used oral calcium supplements, and 14/35 (40 %) used vitamin D supplements. With regard to

Table 1 Clinical variables, calcium and vitamin D supplementation, cumulative corticosteroid dose, and nutritional assessment of the patients with juvenile systemic lupus erythematosus

Variable		Time point 1 (n=35)	Time point 2 (n=35)	P value
Age	Years	15.4±1.8	16.2±1.5	<0.001[a]
SLEDAI	Score	4.0 (0.0; 13.0)	2.0 (0.0; 10.0)	0.137[b]
	>4	16 (45.7 %)	14 (40 %)	0.824[c]
Proteinuria	mg/kg	0.07 (0.02; 4.83)	0.15 (0.03; 0.59)	0.695[b]
CRP	mg/dL	0.6 (0.0; 27.0)	0.9 (0.02; 15.9)	0.642[b]
ESR	mm/first hour	21.5 (6.0; 70.0)	20.0 (2.0; 90.0)	0.313[b]
Calcium intake	Yes	18 (51.4 %)	27 (77.1 %)	0.003[c]
Vitamin D intake	Yes	14 (40.0 %)	25 (71.4 %)	0.001[c]
Cumulative CTC dose	grams	10.6 (5.7; 17.2)[d]	13.8 (8.7; 19.3)[d]	<0.001[a]
Short stature	Z-score	3 (8.6 %)	4 (11.4 %)	0.198[a]
Nutritional status	Normal	19 (54.3 %)	21 (60 %)	0.500[c]
	Overweight	8 (22.8 %)	5 (14.3 %)	0.333[c]
	Obese	8 (22.8 %)	9 (25.7 %)	
Low BMD	Z<−2	15 (42.8 %)	14 (40.0 %)	0.500[c]

SLEDAI Systemic Lupus Erythematosus Disease Activity Index, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *CTC* corticosteroid

[a] Significance level of paired t test

[b] Significance level of Wilcoxon test

[c] Significance level of McNemar's test

[d] Median (interquartile range)

nutritional status, 19/35 (54.3 %) had normal body mass index, 8/35 (22.8 %) were overweight, 8/35 (22.8 %) were obese, and 3/35 (8.6 %) had short stature. Low BMD was found in 15/35 (42.8 %) (Table 1).

None of the variables studied (SLEDAI-2K, interval between assessments, duration of disease, proteinuria, cumulative corticosteroid dose, calcium and vitamin D intake, FMI, LMI, ZBMI) was significantly associated with the change in BC (*data not shown*). There was no correlation between the time after menarche and changes in BC at time point 1 (R=0.06, p=0.73) or time point 2 (R=0.039, p=0.824) (data not shown).

There was no significant difference between time points 1 and 2 with respect to FMI, LMI, or ZBMI (Table 2). In contrast, there was a reduction in bone mineral content over this interval, as demonstrated by the BMD of L1–L4 (−0.027 g/cm^2) and the bone ZH score (−0.260) (Table 2). In the adjusted analysis, lack of supplementation with vitamin D was the only factor significantly associated with the reduction in BMD over the study interval (Table 3).

Discussion

This study showed a decrease in the BMD of postmenarcheal female adolescents with JSLE that was associated with a lack of vitamin D supplementation. A reduction in BMD in female adolescents with JSLE has been reported in several cross-sectional studies, suggesting that the low BMD in these patients is intrinsic to the disease or its treatment [13, 14, 16].

In 1998, Trapani et al. published the first longitudinal study assessing BMD in a small number of children and adolescents (n=15) with JSLE [18]. In contrast to our study, those authors did not observe a significant difference in BMD at assessments performed at two time points with a 1-year interval. Similarly to our study, they did not report any association between BMD and SLEDAI. Trapani et al., in turn, observed a significant and inverse correlation between the cumulative dose of corticosteroids and BMD, and the largest reduction was observed in patients with a cumulative dose of corticosteroids below 10 g. In our study, however, we did not observe a similar correlation [18].

As well as in our study, two prospective studies have reported decreased BMD in JSLE patients after 1-year follow-up [19, 20]. Abdwani et al. evaluated 27 patients whose median age at initial assessment was of 7 years. On the first assessment, the authors reported that all patients had reduced BMD (osteopenia or osteoporosis). In the second evaluation, after 3 years, the proportion of patients with osteoporosis had increased despite daily supplementation of 533 IU of vitamin D. The authors concluded that the worsening of BMD is a common finding in this population although they have not been able to relate it to disease activity, use of immunosuppressant, or serum levels of vitamin D [20].

Lim et al. reported, in a study with 68 JSLE, a general deteriorating trend over time in BMD that could be predicted by a combination of factors namely pubertal status,

Table 2 Variation in BMD (L1–L4), FMI, LMI, and BMI in adolescents with juvenile systemic lupus erythematosus between the two assessment time points

Variable	Unit	Mean (SD)		Mean of the difference (CI 95 %)	*P* value
		Time point 1	Time point 2		
BMD	g/cm^2	0.991 (0.11)	0.964 (0.12)	−0.027 (−0.049; −0.006)	0.011
Bone	Z-score	−1.26 (1.39)	−1.52 (1.31)	−0.260 (−0.463; −0.056)	0.014
BMI	Z-score	0.959 (1.27)	0.786 (1.37)	−0.172 (−0.438; 0.092)	0.193
FMI	kg/m^2	8.474 (3.93)	8.587 (3.89)	0.113 (−0.528; 0.755)	0.722
LMI	kg/m^2	14.327 (1.55)	14.211 (1.62)	−0.116 (−0.480; 0.247)	0.520

BMD bone mineral density from L1 to L4, *g/cm^2* grams per squared centimeter, *CI 95 %* 95 % confidence interval, *BMI* body mass index, *FMI* fat mass index, *LMI* lean mass index

overweight, and cumulative dose of steroids regardless the supplementation of 1000 mg of calcium and more than 800 IU vitamin D daily [19].

Cross-sectional studies on children and adolescents with JSLE have reported contradictory results with regard to the association between the use of corticosteroids and BMD. Some studies have reported the presence of a negative impact [13, 14, 18], while others have not reported a significant effect [14, 17].

With regard to the activity of the disease and BMD, no studies on JSLE have reported a significant association between the SLEDAI and low BMD, which suggests a low sensitivity of the SLEDAI for long-term outcomes such bone-related outcomes. In our sample, 54.2 % of patients had a SLEDAI <4, which characterizes a low level of disease activity at the time of the assessments.

It is well known that the pathogenesis of low BMD and the risk of fractures in SLE are multifactorial [3]. In an attempt to clarify the mechanisms involved, Regio et al. described an association between a reduced BMD and a decrease in lean mass and suggested the importance of muscle rehabilitation as a supportive treatment to reduce the risk of fractures [16]. Although we did not observe a significant reduction in lean mass in our sample, such reductions compared with controls have been reported in some cross-sectional studies [16, 17].

An increase in fat mass in patients with JSLE compared with controls has been reported in the literature [16, 17, 25]. Lilleby et al. reported overweight/obesity in approximately one third of a sample of patients with JSLE. Based on their finding of an increase in fat mass and a pro-atherogenic lipid profile, the authors highlight the high cardiovascular risk in this population [25]. The frequency of excess weight in our study sample was 45.7 %, and although this proportion was higher than the one found by Lilleby et al., there was no significant difference between the two time points. It is noteworthy that patients were cared for by a multidisciplinary team in our outpatient service that included nutritionists and physical therapists, which may explain our findings with respect to BC. Tekano et al. evaluated pediatric patients with rheumatic disease treated with corticosteroids with and without nutritional counseling, and the second group had more weight gain [26].

We observed that lack of vitamin D supplementation was associated with a reduction in BMD in the lumbar spine. Previous studies have shown the high prevalence of vitamin D deficiency in adults and adolescents with SLE [21, 27–33].

Table 3 Variation in BMD in juvenile systemic lupus erythematosus patients between the two assessment time points adjusted for vitamin D, calcium and corticosteroid intake, and disease severity

Variable		Mean (SD)		Mean of the difference	*P* value
		Time point 1	Time point 2	(CI 95 %)	
Vitamin D intake	No (n=21)	0.983 (0.12)	0.956 (0.14)	−0.027 (−0.052; −0.003)	0.027
	Yes (n=14)	1.004 (0.12)	0.975 (0.09)	−0.028 (−0.070; 0.014)	0.182
Calcium intake	No (n=17)	1.007 (0.11)	0.985 (0.13)	−0.021 (−0.047; 0.004)	0.099
	Yes (n=18)	0.977 (0.12)	0.943 (0.12)	−0.033 (−0.069; 0.001)	0.060
Cumulative CTC dose	>13.8 g (n=17)	0.981 (0.12)	0.949 (0.12)	−0.032 (−0.066; 0.001)	0.058
	≤13.8 g (n=18)	1.00 (0.11)	0.097 (0.12)	−0.022 (−0.051; 0.005)	0.107
SLEDAI	>4 (n=14)	0.972 (0.12)	0.941 (0.15)	−0.030 (−0.069; 0.008)	0.113
	≤4 (n=21)	1.004 (0.11)	0.978 (0.10)	−0.026 (−0.052; 0.001)	0.056

CI 95 % 95 % confidence interval, *CTC* corticosteroid, *SLEDAI* Systemic Lupus Erythematosus Disease Activity Index

The use of corticosteroids, recommendations to avoid sun exposure, and kidney impairment are risk factors for this deficiency [21]. Casella et al. recently published a study evaluating the impact of vitamin D deficiency on bone parameters in patients with JSLE. The authors found that deficiency, regardless of vitamin D supplementation, was associated with decreased bone health and increased disease activity. The impact of vitamin D deficiency on bone mass is more pronounced in phases of rapid development such as adolescence [17].

At our outpatient clinic, patients on chronic corticosteroids are provided with calcium and vitamin D supplementation as recommended by the American College of Rheumatology [34]. However, our data suggest that the use of the supplements is not homogeneous because clinical obstacles such as hypercalciuria prevent patients from following these instructions. Another hypothesis is that the low adherence to calcium and vitamin D supplementation could be due to the misunderstanding of the importance of these supplements and excess of medicines that they have to take.

Although our findings of reduced BMD may be attributed to the coefficient of variation of the DXA equipment, it is important to note that our sample consists only of adolescents who should be acquiring bone mass during their development. These data suggest an increased risk for developing bone fragility.

This study has several limitations: retrospective design and lack of evaluation of pubertal stage, frequency of physical exercise, food habits, and biomarkers of bone metabolism. Nevertheless, it is a pioneering study in the longitudinal evaluation of BC and BMD in JSLE. Two other strong points in the present study are the homogeneity of the sample with regard to gender and the fact that all of the adolescents were evaluated postmenarche.

In conclusion, the unfavorable evolution of bone mass in adolescents with JSLE, which is associated with lack of vitamin D supplementation, puts this population at risk for fractures and highlights the importance of developing protocols with a focus on the early diagnosis and treatment of vitamin D deficiency.

Disclosures None.

References

1. Rood MJ, ten Cate R, van Suijlekom-Smit LW et al (1999) Childhood-onset Systemic Lupus Erythematosus: clinical presentation and prognosis in 31 patients. Scand J Rheumatol 28:222–226
2. Hashkes PJ, Wright BM, Lauer MS et al (2010) Mortality outcomes in pediatric rheumatology in the US. Arthritis Rheum 62:599–608
3. Lilleby V (2007) Bone status in juvenile systemic lupus erythematosus. Lupus 16:580–586
4. Müller K, Kriegbaum NJ, Baslund B, Sørensen OH, Thymann M, Bentzen K (1995) Vitamin D3 metabolism in patients with rheumatic diseases: low serum levels of 25-hydroxyvitamin D3 in patients with systemic lupus erythematosus. Clin Rheumatol 14:397–400
5. Lahita RG, Bradlow HL, Ginzler E, Pang S, New M (1987) Low plasma androgens in women with systemic lupus erythematosus. Arthritis Rheum 30:241–248
6. Swaak AJ, van den Brink HG, Aarden LA (1996) Cytokine production (IL-6 and TNF alpha) in whole blood cell cultures of patients with systemic lupus erythematosus. Scand J Rheumatol 25:233–238
7. Tang XL, Qin L, Kwok AW et al (2013) Alterations of bone geometry, density, microarchitecture, and biomechanical properties in systemic lupus erythematosus on long-term glucocorticoid: a case-control study using HR-pQCT. Osteoporos Int 24:1817–1826
8. Tang XL, Griffith JF, Qin L, Hung VW, Kwok AW et al (2013) SLE disease per se contributes to deterioration in bone mineral density, microstructure and bone strength. Lupus 22.11:1162–1168
9. Borba VZ, Matos PG, da Silva Viana PR, Fernandes A, Sato EI, Lazaretti-Castro M (2005) High prevalence of vertebral deformity in premenopausal systemic lupus erythematosus patients. Lupus 14:529–533
10. Bultink IE, Lems WF, Kostense PJ, Dijkmans BA, Voskuyl AE (2005) Prevalence of and risk factors for low bone mineral density and vertebral fractures in patients with systemic lupus erythematosus. Arthritis Rheum 52:2044–2050
11. Helba M, Binkovitz LA (2009) Pediatric body composition analysis with dual-energy X-ray absorptiometry. Pediatr Radiol 39:647–656
12. Castro TC, Terreri MT, Szejnfeld VL et al (2002) Bone mineral density in juvenile systemic lupus erythematosus. Braz J Med Biol Res 35:1159–1163
13. Alsufyani KA, Ortiz-Alvarez O, Cabral DA et al (2005) Bone mineral density in children and adolescents with systemic lupus erythematosus, juvenile dermatomyositis, and systemic vasculitis: relationship to disease duration, cumulative corticosteroid dose, calcium intake, and exercise. J Rheumatol 32:729–733
14. Lilleby V, Lien G, Frey Frøslie K, Haugen M, Flatø B, Førre Ø (2005) Frequency of osteopenia in children and young adults with childhood-onset systemic lupus erythematosus. Arthritis Rheum 52:2051–2059
15. Compeyrot-Lacassagne S, Tyrrell PN, Atenafu E et al (2007) Prevalence and etiology of low bone mineral density in juvenile systemic lupus erythematosus. Arthritis Rheum 56:1966–1973
16. Regio P, Bonfá E, Takayama L, Pereira R (2008) The influence of lean mass in trabecular and cortical bone in juvenile onset systemic lupus erythematosus. Lupus 17:787–792
17. Casella CB, Seguro LP, Takayama L, Medeiros D, Bonfa E, Pereira RM (2012) Juvenile onset systemic lupus erythematosus: a possible role for vitamin D in disease status and bone health. Lupus 21: 1335–1342
18. Trapani S, Civinini R, Ermini M, Paci E, Falcini F (1998) Osteoporosis in juvenile systemic lupus erythematosus: a longitudinal study on the effect of steroids on bone mineral density. Rheumatol Int 18:45–49
19. Lim LS, Benseler SM, Tyrrell PN et al (2012) Predicting longitudinal trajectory of bone mineral density in paediatric systemic lupus erythematosus patients. Ann Rheum Dis 71:1686–1691
20. Abdwani R, Abdulla E, Yaroubi S, Bererhi H, Al-Zakwani I (2015) Bone mineral density in juvenile onset systemic lupus erythematosus. Indian Pediatr 52:38–40
21. Mok CC (2013) Vitamin D, and systemic lupus erythematosus: an update. Expert Rev Clin Immunol 9:453–463
22. Hochberg MC (1997) Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 40:1725
23. de Onis M, Garza C, Victora CG (2003) The WHO Multicentre Growth Reference Study: strategy for developing a new international growth reference. Forum Nutr 56:238–240
24. Khan AA, Bachrach L, Brown JP et al (2004) Standards and guidelines for performing central dual-energy x-ray absorptiometry in premenopausal women, men, and children. J Clin Densitom 7:51–64

25. Lilleby V, Haugen M, Mørkrid L, Frey Frøslie K, Holven KB, Førre O (2007) Body composition, lipid and lipoprotein levels in childhood-onset systemic lupus erythematosus. Scand J Rheumatol 36:40–47
26. Tekano JL, Tucker L, Khattra P (2006) Limiting obesity in children with rheumatic diseases requiring corticosteroid therapy [abstract]. Arthritis Rheum 54:S529
27. Abou-Raya A, Abou-Raya S, Helmii M (2013) The effect of vitamin D supplementation on inflammatory and hemostatic markers and disease activity in patients with systemic lupus erythematosus: a randomized placebo-controlled trial. J Rheumatol 40:265–272
28. Bonakdar ZS, Jahanshahifar L, Jahanshahifar F, Gholamrezaei A (2011) Vitamin D deficiency and its association with disease activity in new cases of systemic lupus erythematosus. Lupus 20:1155–1160
29. Hamza RT, Awwad KS, Ali MK, Hamed AI (2011) Reduced serum concentrations of 25-hydroxy vitamin D in Egyptian patients with systemic lupus erythematosus: relation to disease activity. Med Sci Monit 17:CR711–CR718
30. Kamen DL, Cooper GS, Bouali H, Shaftman SR, Hollis BW, Gilkeson GS (2006) Vitamin D deficiency in systemic lupus erythematosus. Autoimmun Rev 5:114–117
31. Sumethkul K, Boonyaratavej S, Kitumnuaypong T et al (2013) The predictive factors of low serum 25-hydroxyvitamin D and vitamin D deficiency in patients with systemic lupus erythematosus. Rheumatol Int 33:1461–1467
32. Toloza SM, Cole DE, Gladman DD, Ibañez D, Urowitz MB (2010) Vitamin D insufficiency in a large female SLE cohort. Lupus 19:13–19
33. Souto M, Coelho A, Guo C et al (2011) Vitamin D insufficiency in Brazilian patients with SLE: prevalence, associated factors, and relationship with activity. Lupus 20:1019–1026
34. Recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis: 2001 update. American College of Rheumatology Ad Hoc Committee on Glucocorticoid-Induced Osteoporosis. Arthritis Rheum 2001; 44:1496–503